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**Comments: Follow up submission of Signed Declaration and CV for Request for Continued Examination mailed to the USPTO on May 20, 2004.**

Attorney Docket: 22000-2066200  
 Group Art Unit: 1645  
 Examiner: P. A. Duffy  
 Serial No.: 09/830,779  
 Filing Date: November 30, 2001  
 Inventor(s): Kenneth Chin, et al.

Title: A METHOD OF INHIBITION OF PHOSPHOLAMBAN ACTIVITY FOR THE TREATMENT OF CARDIAC DISEASE AND HEART FAILURE

Papers attached:

1. Declaration Under 37 C.F.R. Section 1.132 with CV (11 pages)

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Page 1

Attorney's Docket No.: 22000-20662.00/ SD 99-025

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Kenneth Chien, et al.

Art Unit : 1645

Serial No. : 09/830,779

Examiner : Patricia Ann Duffy

Filed : November 30, 2001

Title : A METHOD OF INHIBITION OF PHOSPHOLAMBAN ACTIVITY FOR THE  
TREATMENT OF CARDIAC DISEASE AND HEART FAILURE

Commissioner for Patents

P.O. Box 1450

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DECLARATION UNDER 37 C.F.R. § 1.132

Sir:

OFFICIAL

1. I, Kenneth Chien, am an expert in the field of molecular biology and cardiac disease and was an expert at the time of the invention. I am a co-inventor of the above-referenced patent application and I am presently employed as a professor at the University of California, San Diego, CA, assignee of the above-referenced patent application. My resume is attached as documentation of my credentials.

2. The specification presents data that demonstrates that PLB inhibitor molecule linked (using, for example, polylysine) to a transport peptide (e.g., an antennapedia transport peptide) can induce enhanced contractility in a cardiac cell. For example, Example 4, pages 28 to 29, provides data that demonstrates that a mutant PLB molecule linked to a transport molecule via polylysine was efficiently translocated into isolated rat cardiomyocytes. These cardiomyocytes showed enhanced contractility. The results of these experiments are illustrated in Figures 5a and 5b.

3. Example 5, including Table 3, pages 29 to 31, of the above-referenced patent application describes experiments that administer a mutant PLB linked to a transport peptide to mouse cardiomyocytes. Table 3 summarizes data from those experiments. As noted on page 31, lines 9 to 11, of Example 5, while there appeared to be a trend towards a larger, faster contraction in the myocyte, T-test analysis did not identify any statistical difference due to the high variability of the data. However, while the results of Example 5's experiments were

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Page 2/3

Applicant : Kenneth Chien, et al.  
Serial No. : 09/830,779  
Filed : November 30, 2001  
Page : 2 of 2

Attorney's Docket No.: 22000-20662.00/ SD 99-025

inconclusive, the totality of the experimental evidence described in this specification overwhelming and conclusively demonstrate that exogenous mutant PLB can inhibit the activity endogenous PBL to improve cardiac contractility. Furthermore, knowledge accrued since the filing of the specification confirms that exogenous mutant PLB can inhibit the activity endogenous PBL to improve cardiac contractility.

4. The level of skill in this art at the time of the invention was very high. Screening procedures used to identify protocols to effectively apply and administer exogenous PLB protein were all well known in the art and at the time this application was filed. Using the teaching of the specification, one skilled in the art could have selected routine screening protocols known in the art at the time of the invention to determine means to effectively apply and administer exogenous PLB protein. Using the teaching of the specification, one of skill in the art could have determined appropriate protocols to apply and administer an exogenous PLB linked to a transport protein to successfully practice the claimed methods of the invention.

5. An exemplary dominant negative PLB is described, *inter alia*, in Example 4, page 28, lines 24 to 26, as a cargo peptide derived from the first 16 residues of PLB, or, SEQ ID NO:8. This cargo sequence could also have been derived from any segment of wild-type PLB or mutant PLB. Determining additional dominant negative PLB species could have been determined by the skilled artisan using routine screening methods, including the exemplary methods described in the specification.

6. The term "dominant negative" was well known in the art at the time of the invention and the specification uses the term as it would have been understood to one skilled in the art at the time of the invention. For example, an example of a textbook definition for "dominant negative protein" now, and at the time of the invention (the definition has not changed) is "a mutant protein that as a result of the mutation has lost activity or function and interferes with the function of its corresponding wild-type protein." Thus, at the time of the invention, and now, the skilled artisan understand that a "dominant negative protein" is a mutant

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Page 3/3

Applicant : Kenneth Chien, et al.  
Serial No. : 09/830,779  
Filed : November 30, 2001  
Page : 3 of 3

Attorney's Docket No.: 22000-20662.00/ SD 99-025

protein that as a result of the mutation has lost activity or function and the mutant protein interferes with the function of its corresponding wild-type protein.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted

Date: \_\_\_\_\_

5/14/04

Chien

Kenneth Chien

## CURRICULUM VITAE

Kenneth Randall Chien, M.D., Ph.D.

**DATE OF BIRTH:** November 24, 1951**HOME ADDRESS:**  
7460 Pepita Way  
La Jolla, Ca 92037  
Phone: (858) 456-6281**PROFESSIONAL ADDRESS:**  
UCSD Institute of Molecular Medicine, 0641  
University of California, San Diego  
La Jolla, CA 92093  
Phone: (858) 534-6835  
FAX: (858) 534-8081  
Email: kchien@ucsd.edu**MARITAL STATUS:** Married (Patricia Ann)**DEPENDENTS:** Daughters (Marisa Court, Elena Brooke)**ACADEMIC BACKGROUND:**

1973 Harvard College, B.A., Cum Laude in Biology

1980 Temple University School of Medicine, M.D., Ph.D.

1980-82 Straight Medicine Internship and Residency, Parkland Memorial Hospital, Dallas, TX

1981-82 Residency in Internal Medicine, Parkland Memorial Hospital, Dallas, TX

1982-84 Clinical and Research Cardiology Fellowship, University of Texas Southwestern Medical Center, Dallas, TX

1984-87 Attending Physician, Cardiology Consult Service and Coronary Care Unit, Parkland Memorial Hospital, Dallas, TX

1984-88 Assistant Professor of Medicine, Cardiology Division, University of Texas Southwestern Medical Center, Dallas, TX

1988-92 Associate Professor of Medicine, Department of Medicine and Member, Center for Molecular Genetics, University of California, San Diego, La Jolla, CA

1992- Professor of Medicine, Department of Medicine and Member, Center for Molecular Genetics, University of California, San Diego, La Jolla, CA

1996-2000 Co-Director, UCSD Cardiovascular Center

1998- Director, UCSD/Salk Program in Molecular Medicine

2000- American Heart Association Endowed Chair in Cardiovascular Research (California Affiliate)

2000- Professor, The Salk Institute (Adjunct)

2000- Director, UCSD Institute of Molecular Medicine

**HONORS AND AWARDS: (Selected)**

1988-93 Established Investigator Award of the American Heart Association

1990- Member, American Society of Clinical Investigation

1991-2001 Editor-in-Chief, *Trends in Cardiovascular Medicine*

1991-96 Director, UCSD American Heart Association, Bugher Foundation Center for Molecular Biology

1991- Director, NHLBI Program Project Grant on Signaling Mechanisms for Cardiac Growth and Hypertrophy

1992-97 Member, Board of Scientific Counselors, National Heart, Lung and Blood Institute, Bethesda, MD

1993- Director, NIH/NHLBI UCSD-Salk Training Program in Cardiovascular Molecular and Cellular Biology

1995- Director, NHLBI SCOR Program on the Molecular Physiology of the Failing Heart

1995- Walter B. Cannon Memorial Award and Lectureship, American Physiological Society

1995- Kaiser Foundation Award and Lectureship

1995- NHLBI Distinguished Service Citation

1996- The Pasarow Foundation Medical Research Award  
(Co-recipients: Stanley B. Prusiner (Neuroscience) and Alfred G. Knudson (Cancer))

1996- American Heart Association - United Way Combined Health Agency Health Hero Award

1998- Robert M. Berne Award and Distinguished Lectureship, American Physiological Society

1998- Robert M. Berne Visiting Professorship, University of Virginia, Charlottesville, VA

1998- Member, The Pasarow Medical Research Foundation Board and Award Committee

1999- Calabresi Visiting Professor and Lectureship, Yale University School of Medicine, New Haven, CT

1999- Bloomfield-Arnold Visiting Professor and Lectureship, Case Western Reserve School of Medicine, Cleveland, OH

1999 Dean's Distinguished Lectureship, University of Medicine and Dentistry in New Jersey, New Brunswick, NJ

1999 Dean's Lecture and Stubenbord Visiting Professorship, Cornell/Rockefeller/ Sloan Kettering M.D.-Ph.D. Program, New York, NY

2000 The 2000 Sankyo Lectureship, Kyoto University, Kyoto, Japan

2000 The Temple University Alumni Achievement Award, Philadelphia, PA

2000 The Brock Lectureship, National Heart and Lung Institute, Imperial College, London, UK

2000 Anna Borun Foundation Visiting Professorship, UCLA School of Medicine, Los Angeles, CA

2000 Annual Visiting Professorship, Institute of Molecular Medicine, Dublin, Ireland

2001 Millennial Lectureship, Loyola University School of Medicine, Chicago, IL

2002 Hans Hecht Lectureship, University of Utah, Salt Lake City, Utah

2003 John Blaffer Lectureship, M.D. Anderson, Houston, Texas

2003 Temple University Alumni Assoc. School of Medicine Certificate of Honor, Philadelphia, PA

2003 2<sup>nd</sup> Annual Arthur C. Fox Visiting Professor in Cardiovascular Biology, NYU, New York, NY

**STUDY SECTIONS/REVIEW COMMITTEES: (Selected)**

1987-91 Member, VA Cardiovascular Merit Review Board

1989-92 Member, Chairman, Selection Committee for AHA Louis Katz Prize in Basic Science

1990-92 Member, Co-Chairman, National AHA Molecular Signaling Study Section

1990-92 Member, Clinical Sciences II, NIH Study Section

1991- 2003 Senior Scientific Advisor/Consultant, Genentech, Inc.

1995- Ad Hoc Reviewer, Wellcome Trust, United Kingdom

1996-99 Councilor, American Society for Clinical Investigation

1997- Member, Scientific Advisory Board (Biotechnology Investment Fund), Pictet and Cie Banquiers, Geneva, Switzerland

1998- Member, The Pasarow Medical Research Foundation Board and Award Committee

1999-2001 Advisor, Integrative Biology Program, Medical Research Council, UK

1999-2000 Member, Pre-Doctoral Fellowship Review Panel, (National Academy of Sciences/ Howard Hughes Medical Institute)

2000-2002 Member, International Advisory Panel, Wellcome Trust, UK

2000- Advisor, Doris Duke Charitable Foundation

Co-Chair, Innovative Clinical Research Awards (2000-2002); Chair, Clinical Interfaces Program (2002- )

2000-02 Scientific Advisor/Consultant, Eli Lilly, USA

2001- Founding Scientist, Celladon, Inc.

2001-2002 Consultant, Scientific Advisory Board, Donald W. Reynolds Foundation

2001- Aviva Biosciences, Scientific Advisory Board, San Diego California

2002- International Scientific Advisory Board, The Baker Institute, Melbourne, Australia

2002- Scientific Advisory Board, Eumorphia, London, UK

2002- Advisor, Helmholtz Foundation, Germany

2003- Scientific Advisory Board, Autogenomics, Carlsbad, CA

#### JOURNAL REVIEWS: (Selected)

<i>Cell</i>	<i>Development</i>
<i>Molecular Cell</i>	<i>Developmental Biology</i>
<i>Developmental Cell</i>	<i>Journal of Biological Chemistry</i>
<i>Nature</i>	<i>Journal of Cell Biology</i>
<i>Nature Genetics</i>	<i>Molecular Endocrinology</i>
<i>Nature Medicine</i>	<i>New England Journal of Medicine</i>
<i>Science</i>	<i>Journal of Clinical Investigation</i>
<i>Proceedings of the National Academy of Science</i>	<i>Genomics</i>
<i>Genes and Development</i>	<i>Circulation Research</i>
<i>Molecular and Cellular Biology</i>	<i>Circulation</i>

#### EDITORIAL BOARDS: (Selected)

1988-91	Associate Editor, <i>Circulation</i>
1992-2001	Member, Editorial Board, <i>Circulation</i>
1991-2001	Editor-in-Chief, <i>Trends in Cardiovascular Medicine</i>
1992-97	Associate Editor, <i>Journal of Clinical Investigation</i>
1998-	Board of Consulting Editors, <i>Journal of Clinical Investigation</i>
2001-	Associate Editor, <i>Development (Development and Disease Section)</i>
2002-	Member, Editorial Board, <i>Journal of Biological Chemistry</i>
2002-	Senior Consultant, Editorial Board, <i>Journal of the American College of Cardiology</i>

#### UNIVERSITY DUTIES:

1988- Attending Physician, UCSD Medical Center

1989- Ph.D. Doctoral Dissertation Review Committee Member for Jason Lam, Valerie Sah, David No, Tara Rachinsky, Carlos Ibanez, John Reece, Dan Rohrer, Kirk Milhoan, Ying Lee, Kim Finley, Ed Monuki, Frank Hong, Sulip Navankassanas, Adrienne Harris, Yimin Zou, Kim Gottshall, Terrie Ramirez, Ruth Yu, Thomas Burkholder, Frank White, John Tozer, Andrew Horvai, Elisc Lamar, Esther Ramos-Merkel, Gina Moore, Ming Yi-Chiang, and Harry Chiu Au.

1995 Member, Steering Committee, Center for Molecular Genetics

1995 Member, UCSD Molecular Medicine Residency Program

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1995 Member, UCSD Science Research Park committee  
 2001 Member, Search Committee for Chair of Medicine  
 2001 Member, Search Committee for Joint Bioengineering Medicine Faculty Position

**SELECTED INVITED LECTURESHIPS:**

**2002**

Keystone Conference on Molecular Biology of the Cardiovascular System, Keystone, Colorado  
 Cold Spring Harbor Conference on Cardiovascular Biology, Cold Spring Harbor, New York  
 Wellcome Trust Conference on Integrative Physiology, Keynote Lecture, London, England  
 Genome Institute of the Novartis Foundation, La Jolla, California  
 Zensun-Fudan University Lecture, Shanghai, China  
 AHA Asian Pacific Conference on Genomics and Heart Disease, Co-Organizer/Chair/Speaker, Honolulu, Hawaii  
 European Society of Cardiology Symposium on Heart Failure, Keynote Lecture, Oslo, Norway  
 Novartis Foundation Symposium on Conduction System Development, London, England  
 University of Oregon Health Sciences Center M.D.-Ph.D. Program, Division of Molecular Medicine, Portland, Oregon  
 EMBO Meeting on Muscle Molecular Biology, Oxford, England  
 UCSF, Grand Rounds, San Francisco, California  
 Hans Hecht Lecture, University of Utah, Salt Lake City, Utah  
 John Blaffer Lectureship, M.D. Anderson, Houston, Texas

**2003**

AAAS Annual Meeting, Symposium Chair/Speaker, Denver, CO 2003

**SELECTED PUBLICATIONS (From a Total of over 210)**

Arber S, Hunter JJ, Ross J Jr, Hongo M, Sansig G, Borg J, Pennard JC, Chien KR, Caroni P: MLP-deficient mice exhibit a disruption of cardiac cytoarchitectural organization, dilated cardiomyopathy, and heart failure. *Cell*. 1997 Feb 7;88(3):393-403.

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Wang Y, Huang S, Sah VP, Ross J Jr, Brown JH, Han J, Chien KR: Cardiac muscle cell hypertrophy and apoptosis induced by distinct members of the p38 mitogen-activated protein kinase family. *J Biol Chem*. 1998 Jan 23;273(4):2161-8.

Chen J, Kubalak SW, Minamisawa S, Price RL, Becker KD, Hickey R, Ross J Jr, Chien KR: Selective requirement of myosin light chain 2v in embryonic heart function. *J Biol Chem*. 1998 Jan 9;273(2):1252-56.

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Chen J, Kubalak SW, Chien KR: Ventricular muscle-restricted targeting of the RXRα gene reveals a non-cell autonomous requirement in cardiac chamber morphogenesis. *Development.* 1998 May;125(10):1943-9.

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Minamisawa S, Gu Y, Ross J Jr, Chien KR, Chen J: A post-transcriptional compensatory pathway in heterozygous ventricular myosin light chain 2-deficient mice results in lack of gene dosage effect during normal cardiac growth or hypertrophy. *J Biol Chem.* 1999 Apr 9;274(15):10066-70.

Marszalek J, Ruiz-Lozano P, Roberts E, Chien KR, Goldstein L: Situs inversus and embryonic ciliary morphogenesis defects in mouse mutants lacking the KIF3A subunit of kinesin-II. *Proc Natl Acad Sci USA.* 1999 Apr 27;96(9):5043-48.

Hirota H, Chen J, Betz UA, Rajewsky K, Gu Y, Ross J Jr, Mueller W, Chien KR: Loss of a gp130 cardiac muscle cell survival pathway is a critical event in the onset of heart failure during biomechanical stress. *Cell.* 1999 Apr 16;97(2):189-98.

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Nakamura T, Ruiz-Lozano P, Lindner V, Yabe D, Taniwaki M, Furukawa Y, Kobuke K, Tashiro K, Lu Z, Andon N, Schaub R, Matsumori A, Sasayama S, Chien KR, Honjo T: DANCE, a novel secreted RGD protein expressed in developing, atherosclerotic, and balloon-injured arteries. *J Biol Chem.* 1999 Aug 6;274(32):22476-83.

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Chien KR: Genomic Circuits and the Integrative Biology of complex Cardiac Diseases. *Nature* 2000 Sep 14;407(6801):227-32.

Pashinforoush M, Poujols P, Peterson KL, Kubalak SW, Ross J Jr, Hefli A, Aebi U, Beckerle MC, Chien KR: Adult mice deficient in actinin-associated LIM-domain protein reveal a developmental pathway for right ventricular cardiomyopathy. *Nat Med.* 2001 May;7(5):591-7.

Giordano FJ, Gerber HP, Williams SP, van Bruggen N, Bunting S, Ruiz-Lozano P, Gu Y, Nath AK, Huang Y, Hickey R, Dalton N, Peterson KL, Ross, J Jr., Chien KR, Ferrara N: A cardiac myocyte vascular endothelial growth factor paracrine pathway is required to maintain cardiac function. *Proc Natl Acad Sci USA.* 2001 May 8;98(10):5780-5.

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Yasukawa H, Hoshijima M, Gu Y, Nakamura T, Praderwand S, Hanada T, Hanakawa Y, Yoshimura A, Ross J Jr, Chien KR: Suppressor of cytokine signaling-3 is a biomechanical stress-inducible gene that suppresses gp130-mediated cardiac myocyte hypertrophy and survival pathways. *J Clin Invest.* 2001 Nov;108(10):1459-67.

Kuo HC, Cheng CF, Clark RB, Lin JJC, Lin JLC, Hoshijima M, Nguyễn-Trần VTB, Gu Y, Ikeda Y, Chu PH, Ross J Jr, Giles WR, Chien KR: A defect in the Kv Channel-Interacting Protein 2 (KChIP2) gene leads to a complete loss of I<sub>to</sub> and confers genetic susceptibility to ventricular tachycardia. *Cell* 107: 801-813, 2001.

Nakamura T, Ruiz-Lozano P, Ikeda Y, Iwanaga Y, Hinek A, Minamisawa S, Cheng CF, Kobuke K, Dalton N, Takada Y, Tashiro K, Ross J Jr, Honjo T, Chien KR: Fibulin-5/DANCE is essential for elastogenesis in vivo. *Nature.* 415:171-5.

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Crone S, Zhao YY, Fan L, Gu Y, Minamisawa S, Peterson KL, Chen J, Kahn R, Condorelli G, Ross J Jr, Chien KR, Lee KF: *ErbB2 is Essential in the Prevention of Dilated Cardiomyopathy*. *Nat Med.* 8:459-465, May 2002.

Ozcelik C, Erdmann B, Pilz B, Wettschureck N, Britsch S, Hubner N, Chien KR, Birchmeier C, Garratt A: *Conditional mutation of the ErbB2 (HER2) receptor in cardiomyocytes leads to dilated cardiomyopathy*. *Proc Natl Acad Sci USA.* Vol 99:13, 8880-8885, June 2002

Hoshijima M, and Chien KR: *Mixed Signals in Heart Failure: Cancer Rules*, *JCI*, 109:849-855, 2002.

Hoshijima M, Ikeda Y, Ross J Jr, Chien KR: *Chronic Inhibition of Heart Failure by a Pseudophosphorylated Mutant of Phospholamban via an In Vivo Cardiotropic rAAV Gene Delivery System*. *Nature Medicine*, 8: 864-871, August 2002.

Chien KR, Olson EN: *Converging Pathways and Principles in Heart Development and Disease*. *Cell.* 110(2):153-62, July 2002.

Zhao YY, Liu Y, Stan RV, Fan L, Gu Y, Dalton N, Chu PH, Peterson K, Ross J Jr, Chien KR: *Defects in caveolin-1 cause dilated cardiomyopathy and pulmonary hypertension in knockout mice*. *PNAS* 2002 99: 11375-11380.

Knöll R, Hoshijima M, Bang M, Yasukawa H, Person V, Lorenzen-Schmidt I, Scott C, Hayashi T, Kimura A, Shiga N, Yokoyama M, Omens J, McKenna N, McCulloch A, Gregorio C, Fuller W, Schaper W, Schaper J, Schultheiss HP, Chien KR: *The Cardiac Mechanical Stretch Sensor Machinery involves a Z Disc Complex that is Defective in a Subset of Human Dilated Cardiomyopathy*. *Cell*, Vol. 111, 943-955, December 27, 2002

Hamblet NS, Lijam N, Ruiz-Lozano R, Wang J, Yang Y, Luo Z, Mei L, Chien KR, Sussman DJ, Wynshaw-Boris A: *Dishevelled 2 is essential for cardiac outflow tract development, somite segmentation and neural tube closure*. *Development*. 2002 129: 5827-5838

Ludwig A, Budde T, Stieber J, Moosmann S, Wahl C, Holthoff K, Langenbach A, Worjik C, Munsch T, Zong X, Feil S, Feil R, Lancel M, Chien KR, Konnerth A, Pape H, Biel M, Hoffmann F: *Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel KCNQ2*. *EMBO J*, Jan 15;22 (2):216-24, 2003.

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Chien, K.R.: *Genotype, Phenotype: Upstairs, Downstairs in the Family of Cardiomyopathies*, *JCI*, 111:175-178, 2003

Cheng, C.F, Kuo, H.C, and Chien, K.R.: *Genetic Modifiers of Cardiac Arrhythmias*, *Trends in Molecular Medicine*, Vol 9:2, 59-66, 2003

Hoshijima, M, Knoell, R, and Chien, K.R.: *Stress Pathways and Heart Failure: The MLP Story*, *Cold Spring Harbor Quantitative Symposium Proceedings*, In Press, 2003

Books:

*Molecular Basis of Cardiovascular Disease*, Editor, K. R. Chien; Section Editors, J. Breslow, J. Leiden, R. Rosenberg, C. E. Seidman, W. B. Saunders Co., Cambridge, MA. (Companion text to E. Braunwald's *Heart Disease*), 1999.

*Molecular Basis of Cardiovascular Disease, Second Edition*, Editor, K.R. Chien; Elsevier Science Publishing Co., 2003, In Press.